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Pat. 7

Patent Form

No. 222911

LETTERS PATENT

ELIZABETH THE SECOND, by the Grace of God Queen of New Zealand and Her Other Realms and Territories, Head of the Commonwealth, Defender of the Faith: To all to whom these presents shall come, Greeting:

WHEREAS pursuant to the Patents Act 1953 an application has been made for a patent of an invention for

QUATERNARY DERIVATIVES OF NOROXYMORPHONE WHICH RELIEVE NAUSEA AND EMESIS

(more particularly described in the complete specification relating to the application)
AND WHEREAS

THE UNIVERSITY OF CHICAGO, an Illinois non-profit corporation, of 947 East 58th Street, Chicago, Illinois 60637, U.S.A.

(hereinafter together with his or their successors and assigns or any of them called "the patentee") is entitled to be registered as the proprietor of the patent hereinafter granted:

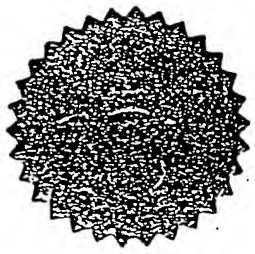
NOW, THEREFORE, We by these letters patent give and grant to the patentee our special licence, full power, sole privilege, and authority, that the patentee by himself, his agents, or licensees and no others, may subject to the provisions of any statute or regulation for the time being in force make, use, exercise, and vend the said invention within New Zealand and its dependencies during a term of sixteen years from the date hereunder written and that the patentee shall have and enjoy the whole profit and advantage from time to time accruing by reason of the said invention during the said term:

AND WE strictly command all our subjects whomsoever within New Zealand and its dependencies that they do not at any time during the said term either directly or indirectly make use of or put into practice the said invention, nor in any way imitate the said invention without the consent, licence, or agreement of the patentee in writing under his hand, on pain of incurring such penalties as are prescribed by law and of being answerable to the patentee according to law for his damages thereby occasioned:

PROVIDED ALWAYS:

(1) That these letters patent shall determine and become void if the patentee does not from time to time pay the renewal fees prescribed by law in respect of the patent:
(2) That these letters patent are revocable on any of the grounds prescribed by the Patents Act 1953 as grounds for revoking letters patent:
(3) That nothing in these letters patent shall prevent the granting of licences in the manner in which and for the considerations on which they may by law be granted:
(4) That these letters patent shall be construed in the most beneficial sense for the advantage of the patentee.

IN WITNESS whereof We have caused these letters patent to be signed and sealed as of the 14th day of December 1987.



PLB

Commissioner of Patents

NOTE — I[illegible] patent is to remain in force, renewal fees must be paid before the expiration of the 4th, 7th 10th, and 1[illegible] year from the date of the patent. Details of relevant fees payable may be obtained from th Patent Office. Such details should be obtained in sufficient time to enable payment to be made before th expiration of the current period.

IN THE MATTER of the Patents Act 1953

LETTERS PATENT

Sealed (Section 27) on

15 MAR 1991

If any person becomes entitled by assignment, transmission or other operation of law to this patent or a part interest therein or to any interest as mortgagee or licensee or otherwise, application must be made to the Commissioner to register such title or interest (see section 84 of the Act).

THE PATENT OFFICE,
LOWER HUTT.

PATENTS FORM NO. 5

PATENTS ACT 1953

COMPLETE SPECIFICATION

QUATERNARY DERIVATIVES OF NOROXYMORPHONE WHICH RELIEVE NAUSEA AND EMESIS

WE, THE UNIVERSITY OF CHICAGO, an Illinois non-profit corporation, of 947 East 58th Street, Chicago, Illinois 60637, U.S.A., hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

(Followed by 1a)

U33:19038/JPG/DAD

QUATERNARY DERIVATIVES OF NOROXYMORPHONE WHICH RELIEVE NAUSEA AND EMESIS

BACKGROUND OF THE INVENTION

The administration of therapeutic doses of morphine and other clinically useful narcotic analgesics is often accompanied by unpleasant side effects on the gastro-intestinal system. For instance, morphine and related opiates such as meperidine and methadone may retard intestinal mobility by causing contractions of the small bowel circular smooth muscle.

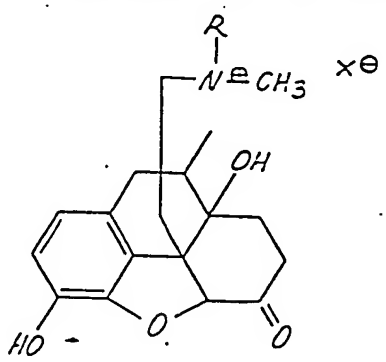
Morphine and related narcotics may also induce nausea and increased mobility of the gastro-intestinal tract resulting in emesis or vomiting. These side effects are caused by direct stimulation of the chemoreceptor trigger zone for emesis in the area postrema of the medulla. (Goodman and Bilman, The Pharmacological Basis of Therapeutics, p. 502 [6th ed. 1980], incorporated herein by reference.) Studies have shown that morphine and other narcotics cause emesis in dogs. For example, Wang and Glaviano, JPET 111:329-334 (9143), incorporated herein by reference, reported that administration of 0.5 mg/kg of morphine intravenously to 12 dogs resulted in emesis in 9 dogs within an average of 2.4 minutes. (Mg/kg refers to milligrams of morphine per kilograms of body weight.) When 1.0 mg/kg of

morphine was administered intramuscularly to 13 dogs, 12 of them vomited within an average time of 3.5 minutes.

SUMMARY OF THE INVENTION

U. S. Patent No. 4,176,186 to myself and others disclosed treatment of intestinal immobility associated with the use of narcotic analgesics through the administration of quaternary derivatives of noroxymorphone. It has now been discovered that the same compounds are also useful for the treatment, both prophylactic and therapeutic, of the nausea and vomiting associated with the administration of these drugs.

According to the invention, therefore, nausea and vomiting by warm-blooded animals receiving morphine and related opiates, meperidine, methadone or the like, may be prevented or relieved by the administration of methylnaltrexone or other quaternary derivatives of noroxymorphone represented by the formula:



wherein

R is allyl or a related radical such as chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion.

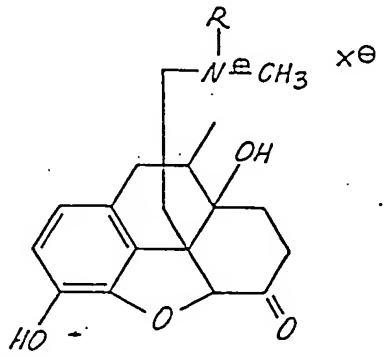
These compounds are administered to the animal either prior to or simultaneously with the administration of the narcotic analgesic. They may be

administered either enterally or parenterally. There has not been observed any interference with the analgesic activity of the opiates.

As used herein, unless the sense of the usage indicates otherwise, the term "morphine" refers to any narcotic analgesic.

DETAILED DESCRIPTION

This invention relates to the use of quaternary derivatives of noroxymorphone to prevent or relieve nausea and vomiting associated with the administration of morphine to warm-blooded animals. The useful compounds are represented by the formula:



wherein

R is allyl or a related radical such as chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion.

The compounds are synthesized as described in United States Patent No. 4,176,186, the disclosure of which is incorporated herein by reference. A particularly preferred noroxymorphone derivative is methylnaltrexone, but other compounds represented by the above formula are also suitable.

Methylnaltrexone or other noroxymorphone derivatives may be administered to the patient either

enterally or parenterally. However, a preferred method of administration is by injection. Nausea and emesis may follow after even a single does of morphine, unlike intestinal immobility which is usually the effect of chronic repeated usage of the drug. Consequently, it is contemplated that the patient will be given an injection of methylnaltrexone prior to surgery or other occasion when morphine is used to treat acute pain.

As illustrated by the following Controls and Examples, our studies show that methylnaltrexone inhibits emesis when administered either together with the morphine or before the morphine is administered. It is thought that methylnaltrexone or other quaternary noroxymorphone derivatives may be administered up to two hours before the administration of morphine, but that period may be variable. In our studies, methylnaltrexone was administered intramuscularly by means of a syringe. Methylnaltrexone may also be administered enterally or parenterally by other means. It has been found to be effective in dosages in the range of about 0.05 mg/kg to about 1.0 mg/kg for each 1 mg/kg of administered morphine. It was found effective when administered in the same syringe as morphine and also when administered up to about one hour before the administration of morphine.

The effect of methylnaltrexone in reversing the emetic effects of morphine is illustrated herein. The unit of mg/kg refers to milligrams of substance administered per kilograms of body weight.

CONTROL 1 AND EXAMPLE 1

One mg/kg of morphine was administered intramuscularly to five dogs. Four dogs vomited. In each instance, vomiting occurred within four minutes. On a different day the same dose of morphine was

administered intramuscularly to the same five dogs in the same syringe with 1 mg/kg of methylnaltrexone. None of the dogs vomited.

CONTROL 2 AND EXAMPLE 2

Six dogs were given intramuscular doses of 1 mg/kg of morphine. All six dogs vomited. On an additional day the same dose of morphine was combined with 0.5 mg/kg of methylnaltrexone and administered in the same syringe to the same dogs. None of the dogs vomited.

CONTROL 3 AND EXAMPLE 3

One mg/kg of morphine was administered intramuscularly to three dogs. All three dogs vomited. On an additional day the morphine was combined with 0.25 mg/kg of methylnaltrexone and administered in the same syringe. None of the dogs vomited.

CONTROL 4 AND EXAMPLE 4

Methylnaltrexone was administered to two dogs prior to the administration of 1 mg/kg morphine. In one dog, 0.5 mg/kg of methylnaltrexone was administered intramuscularly 15 minutes before the morphine. No vomiting occurred. In the second dog, the same dose of methylnaltrexone was administered 30 minutes before the administration of morphine. No vomiting occurred.

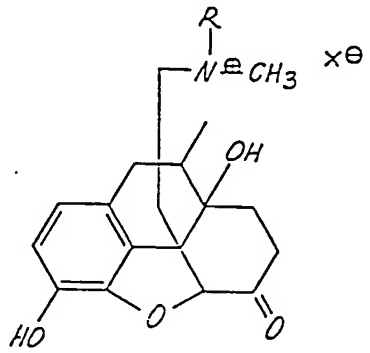
CONTROL 5 AND EXAMPLE 5

0.05 mg/kg methylnaltrexone was administered intravenously to four dogs one minute prior to the administration of 1.0 mg/kg morphine. No vomiting occurred in any of the dogs. On a different day, the same animals were given 1.0 mg/kg morphine without the administration of methylnaltrexone. All four dogs vomited.

The administration of methylnaltrexone alone was found to produce no noticeable effects in the animals. Previous studies with larger doses of methylnaltrexone have demonstrated that unlike the non-quaternary naltrexone, methylnaltrexone does not precipitate withdrawal systems in morphine-tolerant dogs. Russell et al., Eur. J. Pharmacol. 78:255-261 (1982), incorporated herein by reference. Methylnaltrexone has not been found to interfere with the analgesic activity of morphine or narcotics.

WHAT WE CLAIM IS:

1. A method for preventing or relieving nausea and emesis associated with the use of narcotic analgesics in warm-blooded animals, which comprises administering to an animal prone towards nausea or emesis on receiving narcotic analgesics, an effective amount of at least one nausea and emesis relieving compound of the formula:



wherein

R is allyl or a related radical such as chloroallyl, cyclopropyl-methyl or propargyl, and

X is the anion of an acid, especially a chloride, bromide, iodide or methylsulfate anion, prior to or simultaneously with administration of the narcotic analgesic.

2. A method as claimed in claim 1, where the compound is administered to the animal in an amount between about 0.05 mg/kg and about 1.0 mg/kg.

3. A method as claimed in claim 1, where the compound is administered to the animal enterally.

4. A method as claimed in claim 1, where the compound is administered to the animal parenterally.

5. A method as claimed in claim 4, where the compound is administered to the animal by injection.

6. A method as claimed in claim 1, where the compound is administered to the animal prior to the administration of the narcotic analgesic.

7. A method as claimed in claim 6, where the compound is administered to the animal up to about two hours prior to the administration of the narcotic analgesic.

8. A method as claimed in claim 1, where the compound is administered to the animal concurrently with the administration of the narcotic analgesic.

9. A method as claimed in claim 1, where the compound comprises methylnaltrexone.

10. A method for preventing or relieving nausea and emesis associated with the use of narcotic analgesics in warm-blooded animals, which comprises administering to an animal prone to exhibit nausea or emesis on administration of narcotic analgesics, methylnaltrexone in the amount of between about 0.05 mg/kg and about 1.0 mg/kg simultaneous with or up to about two hours prior to the time of administration of the narcotic analgesic.

11. A method as claimed in claim 10, where the methylnaltrexone is administered to the animal parenterally.

12. A method for preventing or removing nausea and emesis substantially as hereinbefore described with reference to any one of Examples 1 to 5.

THE UNIVERSITY OF CHICAGO
by their authorized agents
P.L. BERRY & ASSOCIATES
per: